

Target Specific Oral Anticoagulants (TSOACs) Rivaroxaban (Xarelto) and Apixaban (Eliquis)

Criteria for Use for Venous Thromboembolism (VTE) Prophylaxis for Total Hip or Total Knee Replacement Surgery February 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE OUTSIDE THE RECOMMENDATIONS SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

The Product Information should be consulted for detailed prescribing information. The VA National PBM-MAP-VPE TSOAC Class Review, individual Drug Monographs and CFU for Stroke Prevention in Atrial Fibrillation (AF) and VTE treatment are available at www.pbm.va.gov or <https://vaww.cmopnational.va.gov/cmop/PBM/default.aspx>

VTE PROPHYLAXIS OPTIONS

TSOACs are one of several options available including low molecular weight heparin, fondaparinux, warfarin, heparin, aspirin, or nonpharmacologic devices. This TSOAC CFU document is intended to help appropriately select patients where use of a TSOAC is desired.

EXCLUSION CRITERIA (if ONE is checked, patient is not eligible)

- ☐ At high risk of or active pathological bleeding
- ☐ Known significant liver disease (e.g., acute clinical hepatitis, chronic active hepatitis, cirrhosis, liver function test [LFT] elevations >2-3x upper limit of normal, Child-Pugh B or C or any hepatic disease associated with coagulopathy)
- ☐ Estimated creatinine clearance (CrCl) <30 ml/min
- ☐ Concomitant therapy with combined P-glycoprotein (P-gp) and strong CYP 3A4 inhibitors (e.g., itraconazole, ketoconazole, indinavir/ritonavir, lopinavir/ritonavir, ritonavir, and conivaptan) (See Issues for Consideration)
- ☐ Concomitant therapy with strong dual P-gp and CYP 3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) (See Issues for Consideration)
- ☐ Active endocarditis
- ☐ Previous hypersensitivity reaction to the TSOAC
- ☐ Epidural/spinal anesthesia (see Issues for Consideration)
- ☐ Pregnancy (i.e., known pregnancy or positive pregnancy test)

INCLUSION CRITERIA (ALL must be selected for patient to be eligible)

- ☐ VTE prophylaxis when pharmacologic therapy is indicated for planned total hip or total knee arthroplasty
- ☐ Renal function assessment (CrCl) (see Monitoring for additional information)

For women of childbearing potential:

- ☐ Pregnancy should be excluded prior to receiving TSOAC and the patient provided contraceptive counseling on potential risk vs. benefit of taking a TSOAC if patient were to become pregnant

DOSAGE AND ADMINISTRATION

- **Rivaroxaban:** The recommended dose of rivaroxaban is 10 mg once daily with or without food, initiated at least 6 to 10 hours after surgery once hemostasis is established.
- **Apixaban:** The recommended dose of apixaban is 2.5 mg twice daily started 12 to 24 hours after surgery once hemostasis is established.
- Consult prescribing information for additional information.

MONITORING

- Patients should be monitored for signs and symptoms of bleeding and other adverse effects.
- Renal function and blood counts (e.g., complete blood count, platelets) should be assessed at baseline and periodically as appropriate.
- No routine laboratory monitoring of anticoagulant activity is recommended.

ISSUES FOR CONSIDERATION

- **Indications for use:** Use of rivaroxaban and apixaban for VTE prophylaxis should be limited to patients undergoing total hip or knee arthroplasty, as the benefits in other clinical settings have not been established. Note that dabigatran (Pradaxa) is not FDA approved for VTE prophylaxis and is not recommended. (See additional PBM CFU documents for information on use for other indications)
- **Bleeding:** The primary risk with TSOACs is bleeding. Rates of major bleeding were low in clinical trials. Apixaban was not associated with increased bleeding rates. There was a tendency towards more bleeding events with rivaroxaban compared with enoxaparin when data from individual studies were pooled.
- **Spinal/Epidural Hematoma:** Like other anticoagulants, rivaroxaban and apixaban labeling includes a boxed warning on the risk of spinal/epidural hematoma when the drug is used in patients receiving neuraxial anesthesia or undergoing spinal puncture. Long-term or permanent paralysis may result. See package label for additional information.
- **Reversal of anticoagulant effects:** There are no specific reversal agents for the TSOACs, although the drugs have a relatively short duration of action. Information on the optimal management of bleeding on TSOACs is lacking. Management should be individualized according to the specific situation but may reasonably include discontinuation of treatment and implementation of supportive measures (compression, surgical hemostasis, transfusion). Dialysis is not expected to be effective for removal of rivaroxaban or apixaban.
- **Renal impairment:** Rivaroxaban is eliminated partially through the kidneys and is expected to cause increased exposure and pharmacodynamic effects in patients with renal impairment. Rivaroxaban should be avoided in patients with severe renal impairment (CrCl <30 ml/min) and discontinued in patients who develop acute renal failure while taking the drug. Patients with moderate renal impairment should be monitored closely for signs and symptoms of bleeding. Apixaban undergoes less renal elimination and should still be avoided in patients with a CrCl <30

ml/min since these patients were excluded from clinical trials. Patients with fluctuating renal function should be monitored more frequently for bleeding issues or alternative anticoagulant considered.

- **Pregnancy:** PBM recommends generally avoiding the TSOACs during pregnancy because of the potential for pregnancy related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible.
- **Combined P-gp and/or strong CYP3A4 inducer interactions:** Concomitant use of rivaroxaban or apixaban with dual P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) results in reduced TSOAC exposure (and potentially reduced efficacy) and should be avoided.
- **Combined P-gp and/or CYP3A4 inhibitor interactions:** Concomitant use of rivaroxaban or apixaban with dual P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan) increases TSOAC exposure, may increase bleeding risk, and should be avoided.
- **Duration of therapy:** The recommended duration of prophylaxis for knee replacement is 12 days and for hip replacement is 35 days.
- **Pharmacodynamic Interactions:** Concomitant use TSOACs and medications that affect hemostasis are expected to increase the risk of bleeding (aspirin, anti-platelet agents, other anticoagulants, fibrinolytics, NSAIDs). Avoid the use of rivaroxaban or apixaban for VTE prophylaxis with additional anticoagulants due to the increased bleeding risk. The expected increased risk of bleeding in combining rivaroxaban or apixaban with other agents that affect hemostasis (e.g., anti-platelets, NSAIDs, etc.) should be considered when prescribing.
- **Interruptions in therapy:** Recommendations on discontinuing therapy for surgery or invasive procedures to reduce the risk of bleeding is provided in the prescribing information. If possible, TSOACs should be discontinued at least 24 hours prior to surgery or invasive procedures with an increased bleeding risk. Discontinuations of longer durations are recommended for surgery and procedures with a higher bleeding risk where complete hemostasis is required and for patients with renal impairment. For urgent/emergent interventions, the increased risk of bleeding should be weighed along with the risks of delaying the procedure. The TSOAC should be restarted as soon as adequate hemostasis is achieved following the procedure. If oral medications cannot be used following the procedure, an injectable anticoagulant may be considered.
- **Efficacy vs. enoxaparin 30 mg twice daily in TKR:** Apixaban did not meet prespecified noninferiority criteria compared to the U.S. dose of enoxaparin 30 mg twice daily when evaluated for VTE prophylaxis in TKR in ADVANCE-1 (primary outcome events occurred in 9% of apixaban patients and 8.8% of enoxaparin patients). Rivaroxaban was compared to 30 mg enoxaparin twice daily for VTE prophylaxis in TKR (in the RECORD-4 trial); however, as reported by the FDA, there were significant concerns about study conduct, oversight and data collection, limiting the confidence in the results. When studied against the European enoxaparin dose of 40 mg once daily in TKR, both apixaban and rivaroxaban maintained efficacy.